

I. General Information

CAS Number: 94-60-0*
 Name: 1,4-Cyclohexanedicarboxylic acid, dimethyl ester
 Dimethyl cyclohexane-1,4-dicarboxylate
 Dimethyl-1,4-cyclohexanedicarboxylate
 Dimethyl hexahydrotetraphthalate
 DMCD (mixed isomers)

* This CAS No. is a mixture of both *cis*- and *trans*- isomers. The chemical CAS number used for some tests was 3399-22-2, which corresponds to a pure *trans*- isomer of DMCD.

II. Physical-Chemical Data

A. Melting Point

Test Substance Test substance: Remarks:	DMCD (mixed isomers); CAS No.: 94-60-0
Method Method: Remarks:	Estimation
Results Melting point value: Remarks:	-46.41 °C Data is a mean of both estimation methods
References	MPBPWIN v1.40; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.10, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

B. Boiling Point

Test Substance Test substance: Remarks:	DMCD (mixed isomers); CAS No.: 94-60-0 Purity unknown
Method Method: GLP: Year:	Not Specified Unknown Unknown
Results Boiling point value: Pressure: Remarks:	265 °C (mixed isomer) Not stated Primary reference was not obtained.
References	Lewis, R.J., Sr (Ed.). Hawley's Condensed Chemical Dictionary. 12th ed. New York, NY: Van Nostrand Rheinhold Co., 1993, 415.
Other	Data obtained from Hazardous Substances Data Bank Number: 5284. Last revision date: 20010809.

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C. Vapor Pressure

Test Substance Test substance: Remarks:	DMCD (mixed isomers); CAS No.: 94-60-0
Method Method: Remarks:	Estimation Modified Grain method and Antoine method. Results are a mean of both methods.
Results Vapor pressure value: Temperature: Remarks:	0.0822 mmHg 25 °C
References	MPBPWIN v1.40; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.10, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

D. Partition Coefficient

Test Substance Test substance: Remarks:	DMCD (mixed isomers); CAS No.: 94-60-0
Method Method: Remarks:	Estimation
Results Log K _{OW} : Remarks:	2.11
References	KOWIN v1.66; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.10, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

E. Water Solubility

Test Substance Test substance: Remarks:	DMCD (mixed isomers); CAS No.: 94-60-0
Method Method: Remarks:	Estimation
Results Value: Temperature: Description: Remarks:	688.7 mg/L 25 °C Slight A K_{ow} of 2.11 was used in the estimation
References	WSKOW v1.40; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.10, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

III. Environmental Fate Endpoints

A. Photodegradation

Test Substance Test substance: Remarks:	DMCD (mixed isomers); CAS No.: 94-60-0
Method Method: Test type: Remarks:	Estimation Atmospheric oxidation
Results Temperature: Hydroxyl radicals reaction OH Rate constant: Half-life Ozone reaction: Remarks:	25 °C 7.9071 x 10 ⁻¹² cm ³ /molecule-sec 1.35 Days (12-hr day; 1.5x10 ⁶ OH/cm ³) No ozone reaction estimation
Conclusions	Material is oxidized at a moderate rate by hydroxyl radicals in the atmosphere.
Data Quality Remarks:	
References	AopWin v1.90; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.10, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

B. Stability in Water

Test Substance Test substance: Remarks:	DMCD (mixed isomers); CAS No.: 94-60-0 Test material is an ester compound
Method Method: Test type: Temperature: Remarks:	Estimation Aqueous base/acid-catalyzed hydrolysis 25 °C
Results Total K _b for pH >8: Half-life (pH 8): Half-life (pH 7): Remarks:	2.423 x 10 ⁻² L/mol-sec 331.018 days 9.063 years Material is not likely to be hydrolyzed by surface water.
References	HYDROWIN v1.67; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.10, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

C. Biodegradation

Test Substance Test substance: Remarks:	DMCD (<i>trans</i> isomer); CAS No.: 3399-22-2 Purity was 99.9%
Method Method: Test type: GLP: Year: Contact time: Inoculum: Remarks:	OECD: TG-301B and Annex V C.5 Ready biodegradation using the CO ₂ evolution test (Modified Sturm) Yes 1991 35-days Activated sludge microorganisms (unacclimated) Activated sludge was obtained from Van Lare Treatment plant in Rochester NY. Four inoculated carboys were used: one for the inoculum blank, one for a positive control (sodium benzoate), and two containing test article (tested at 10 and 20 mg/L). Microbe count of supernatant was 10 ⁷ organisms/ml.
Results Total degradation at test end (Day 35): Time for 10% degrad.: Does study meet 10-day window criteria: Classification: Breakdown products: Remarks:	81% (10 mg/L) and 79% (20 mg/L) 11 days No Results indicate material was not readily degraded (>60%) within the 10-day time frame Not determined No significant amount of CO ₂ was evolved from inoculum blank. The positive control reached 60% degradation by Day 8 and 79% by test end (DOC loss was therefore 98%). DMCD was not readily biodegradable according to the definitions of this test which requires >60% degradation within the time window of 10 days, counting from the day that the observed level of biodegradation first exceeds 10%. Instead, DMCD was only degraded 54% (10 mg/L) and 48% (20 mg/L) in this time frame but considerable biodegradation did occur, however, based on 60% degradation within a 12-day time window. The end of the test on Day 35 observed 81% biodegradation of DMCD at 10 mg/L and 79% at 20 mg/L. On Day 28 material was approximately 75% degraded.
Conclusions	These data indicate DMCD is unlikely to persist in the environment but it may not be fully removed during wastewater treatment.
Data Quality Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Ready Biodegradability (Modified Sturm); Environmental Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-105-043461-1, November 14, 1991.
Other	An activated sludge respiration inhibition test was conducted on <i>trans</i> -DMCD following OECD guidelines 209/1988 Annex V supplement and GLP assurances. Results determined the NOEC to be 1000 mg/L (highest dose tested). [Environmental Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-620-043461-1, August 1991.

D. Transport between Environmental Compartments (Fugacity)

Test Substance Test substance: Remarks:	DMCD (mixed isomers); CAS No.: 94-60-0										
Method Test type: Model used: Remarks:	Estimation Level III Fugacity Model; EPIWIN:EQC from Syracuse Research Corporation										
Results Model data and results: Estimated distribution and media concentration (levels II/III): Remarks:	<table><tr><th colspan="2">Distribution (%)</th></tr><tr><td>Air</td><td>1.32</td></tr><tr><td>Water</td><td>35.6</td></tr><tr><td>Soil</td><td>63.0</td></tr><tr><td>Sediment</td><td>0.119</td></tr></table> <p>Physical chemical values utilized in this model were default values obtained from the EPIWIN program.</p>	Distribution (%)		Air	1.32	Water	35.6	Soil	63.0	Sediment	0.119
Distribution (%)											
Air	1.32										
Water	35.6										
Soil	63.0										
Sediment	0.119										
Conclusions											
Data Quality Remarks:											
References	Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.10, Syracuse Research Corporation, Syracuse, New York 13210. The Level III model incorporated into EPIWIN is a Syracuse Research Corporation adaptation of the methodology described by Mackay <i>et al.</i> 1996; <i>Environ. Toxicol. Chem.</i> 15 (9), 1618-1626 and 1627-1637.										
Other											

IV. Ecotoxicity

A. Acute Toxicity to Fish

<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Analytical monitoring:</p> <p>Exposure period: Remarks:</p> <p>Results Nominal concentration: Measured concentration: Endpoint value: Biological observations:</p> <p>Statistical methods: Remark:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>DMCD (<i>trans</i> isomer); CAS No.: 3399-22-2 Purity was 99.9%</p> <p>EPA 600/3-75-009 and 600/4-85/013, 3rd Ed. Acute: Static w/ renewal at 48 hours No 1991 Fathead minnow (<i>Pimephales promelas</i>) Yes; temperature (24 ± 1 °C), pH (7.7 – 8.0), dissolved oxygen (6.0 – 5.4 mg/L), alkalinity (50 mg/L), hardness (116 mg/L), conductivity (312 – 327 umhos/cm) 96-Hours Moderately hard reconstituted water used as control and dilution water. Two replicates of 500 mL solution in 1000 mL glass beakers containing 10, 48-day old fish used per treatment level. Test was conducted in replicate.</p> <p>10, 18, 32, 56, 100 mg/L Not measured 96-hour $LC_{50} = 23$ mg/L No mortality was observed throughout the 96-hour exposure in the control. Several fish at the 18 and 32 mg/L treatment level exhibited loss of equilibrium and respective mortality rates of 10 and 95% . Trimmed Spearman-Kärber Method Although concentrations were not measured, data from the algae study suggest the material remains in the test solution and does not volatilize or degrade.</p> <p>The 96-hour LC_{50} value indicates that the test substance would be classified as “harmful to aquatic organisms” according to the European Union’s labeling directive and would correspond to a “moderate concern level” according to the U.S. EPA’s assessment criteria.</p> <p>Reliable with restrictions This was a well-documented study conducted using USEPA methodology but without concentration verification of test material.</p> <p>Aquatic Toxicity of Trans-DMCD to <i>Pimephales promelas</i>, <i>Daphnia magna</i>, and <i>Ceriodaphnia dubia</i>; Young-Morgan & Associates, Franklin, Tennessee; August 1991.</p>
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B. Acute Toxicity to Aquatic Invertebrates

Test Substance	
Test substance:	DMCD (<i>trans</i> isomer); CAS No.: 3399-22-2
Remarks:	Purity was 99.9%
Method	
Method:	EPA 600/3-75-009 and 600/4-85/013, 3rd Ed.
Test type:	Acute
GLP:	No
Year:	1991
Species/strain:	<i>Daphnia magna</i>
Analytical monitoring:	Yes; temperature (24 ± 1 °C), pH (7.7 – 7.9), dissolved oxygen (8.0 – 8.1
Exposure period:	mg/L), alkalinity (44 mg/L), hardness (82 mg/L), conductivity (297
Test details:	umhos/cm)
Remarks:	48-Hours
Results	
Nominal concentration:	10, 18, 32, 56, & 100 mg/L
Measured concentration:	Not measured
Endpoint value:	48-hour $LC_{50} > 100$ mg/L
Biological observations:	Only one mortality in the 100 mg/L treatment was observed in the test. No
	mortality was observed in the control or other treatment levels
Statistical methods:	NA
Remarks:	Although concentrations were not measured, data from the algae study
Conclusions	
	The 48-hour LC_{50} value indicates that the test substance would not be
	classified according to the European Union's labeling directive and would
	correspond to a "low concern level" according to the U.S. EPA's assessment
	criteria.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	This was a well-documented study conducted using USEPA methodology but
References	
	Aquatic Toxicity of Trans-DMCD to <i>Pimephales promelas</i> , <i>Daphnia magna</i> ,
	and <i>Ceriodaphnia dubia</i> ; Young-Morgan & Associates, Franklin, Tennessee;
	August 1991.
Other	

C. Toxicity to Aquatic Plants

Test Substance Test substance: Remarks:	DMCD (mixed isomers); CAS No.: 94-60-0 Purity was 92.9% by weight determined by GC/FID. Structure confirmed by mass spectrometric detection
Method Method: Test type: GLP: Year: Species/strain: Endpoint basis: Exposure period: Analytical procedures: Remarks:	OECD: TG-201 Growth inhibition of algae Yes 2003 <i>Selenastrum capricornutum</i> Cell concentrations (biomass) and growth rate 72-hours Temperature, light intensity, rpm, and test substance concentration were assessed at the 0, 24, 48, and 72 hours. The pH was assessed at time 0 and after 72 hours. The concentration of algae at Day 0 was 10^4 cells/ml.
Results Nominal concentration: Measured concentration: Endpoint value: NOEC or LOEC: Was control response satisfactory: Statistical Methods: Remarks:	125 mg/L 124.6 mg/L (geometric mean) E_bC_{50} and E_rC_{50} (0-72 hr) > 124.6 mg/L 72-hour NOEC = 124.6 mg/L Yes (a 129.9 fold increase in cell number was observed within 3 days) NA, The statistical analysis of the data was not necessary as inhibition in biomass or growth rate was not observed. A mean illumination of 741 foot-candles was maintained. The mean temperature was 24°C and pH ranged from 7.56 to 7.88. Cultures were oscillated at 100 rpm. Test substance and cell concentrations were determined at test initiation and at 24-hour intervals during the test. The exposure concentration was calculated as the geometric mean of the test substance solutions analyzed at test start and at 24-hour intervals. The test substance was stable under the conditions of the test as 2.98% loss was observed over 72 hours. No protocol deviations were noted.
Conclusions	The 72-hour E_bC_{50} and NOEC values indicate that, based on this study, the test substance would not be classified according to the European Union's labeling directive and would be classified as a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality Reliability: Remarks:	Reliable without restrictions This was a well-documented OECD-study conducted under GLP assurances
References	A Growth Inhibition Test with the Alga, <i>Selenastrum capricornutum</i> ; Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-512-907570-A; February 26, 2003.
Other	

V. Toxicological Data

A. Acute Toxicity

Test Substance Test substance: Remarks:	DMCD (mixed isomers); CAS No.: 94-60-0 Purity was not noted in report
Method Method: Test type: GLP: Year: Species/strain: Route of exposure: Dose levels: Remarks:	OECD TG-401 (Annex V, test B.1) Acute lethality; LD ₅₀ estimate Yes 1996 Rat/CD(SD)BR VAF/Plus Oral gavage 2,500, 4,000, and 5,000 mg/kg There were five/sex at 5,000 mg/kg and 5 females for 2,500, 4,000 mg/kg. Animals were 7-8 weeks in age and weighed between 200-214 (males) and 155-184 (females) grams. Material was administered as a neat liquid. The LD ₅₀ value was determined by Weil, C.S. (1952).
Results Value: Deaths at each dose: Remarks:	LD ₅₀ was >5,000 mg/kg (males) and approx. 2812 mg/kg for females 5,000 mg/kg: 2 males (Day 1) and 5 females (4 on Day 1 and 1 on Day 2). Animals showed slight to severe weakness with prostration and diarrhea on Day 0. By Day 2 all surviving males appeared clinically normal. 4,000 mg/kg: 3/5 died on Day 1 and the other 2 died on Day 2. On day 0, animals exhibited slight to moderate weakness progressing to moderate weakness with reduced feces by Day 2. 2,500 mg/kg: 1/5 died on Day 1. Day 0, one animal exhibited slight weakness while all the others were clinically normal throughout the study. A gain in weight was reported for all survivors after the 2-week study observation period was complete. The cause of death for the rats was not determined although results of the gross necropsies indicated evidence of gastric irritation.
Conclusions	Material would be considered as slightly toxic.
Data Quality Reliability: Remarks:	Reliable without restrictions The study followed established guidelines and was conducted under GLP assurances.
References	Dimethyl-1,4-cyclohexanedicarboxylate, mixed isomer acute oral toxicity in the rat. Eastman Kodak Company, Rochester, NY; HAEL No.: 95-0212; January 9, 1996.
Other	The results of an acute toxicity study conducted on the <i>trans</i> isomer of DMCD (CAS No. 3399-22-2) indicated the LD ₅₀ as >3,200 mg/kg for both sexes with no evidence of toxicity. [Basic toxicity of <i>trans</i> -Dimethyl-1,4-cyclohexanedicarboxylate; Eastman Kodak Company, Rochester, NY; HS&HFL No.: 80-0296; February 18, 1981

B. Repeated Dose Toxicity

Test Substance Test substance: Remarks:	1,4-Cyclohexanedicarboxylic acid (CHDA; CAS No.: 1076-97-7) Purity was 99.0%
Method Method: Test type: GLP: Year: Species/strain: Route of exposure: Duration of test: Exposure levels: Sex: Exposure period: Post-exposure observation period: Remarks:	OECD: TG-407 and Annex V B.7 Repeated oral-dose toxicity Yes 1988 Rat/Sprague-Dawley (CD(SD)BR) Oral 4-weeks 0, 0.1, 0.3, and 1.0% in diet Both (5/sex) Continuous in feed for 29 days None Rats, were approximately 6-7 weeks in age and weighed 177 g (males) and 143 g (females) at study initiation. Animals were weighed and had detailed clinical observations recorded on Days 0, 4, 7, 14, 18, 22, and 29. Feed intake was assessed twice/week. At termination hematology (Hb conc., Hct, RBC count and morphology, WBC count and diff., and plt. Count) and clinical chemistries (AST, ALT, SDH, ALK, Creat., BUN, and gluc.) were conducted. At termination, animals underwent a gross examination with the following organs weighed: liver, spleen, kidneys, adrenals, testes, and thymus. Organs examined by histology included: trachea, lungs, heart, esophagus, stomach, sm. & lg. intestine, pancreas, liver, salivary glands, kidney, urinary bladder, pituitary, adrenals, thyroids, parathyroids, thymus, spleen, mesenteric lymph nodes, bone marrow, brain, testes, epididymis, accessory sex organs in males, fallopian tubes, uterus, vagina and ovaries.
Results NOAEL (NOEL): Actual doses received: Toxic responses by dose: Statistical methods: Remarks:	1.0%; [871 mg/kg (males) and 894 mg/kg (females)] Males: 0, 81, 246, 871 mg/kg; Females: 0, 86, 259, 894 mg/kg There were no mortalities or clinical signs related to exposure. There were no differences in body weights, feed consumption, hematology, clinical chemistries, and organ weights compared to controls. There were no gross or histological changes observed. Mean values of most data were evaluated for homogeneity by Bartlett's test and significance assessed using ANOVA and Duncan's multiple range test.
Conclusions	CHDA induced essentially no toxicity following 4 weeks of exposure at a high exposure rate (1% of diet).
Data Quality Reliability: Remarks:	Reliable without restrictions This is a well-documented study that followed OECD guidelines and was conducted under GLP assurances.
References	Four-Week Oral Toxicity Study of 1,4-Cyclohexanedicarboxylic Acid in the Rat. Eastman Kodak Company, Rochester, NY; HAEL No.: 87-0082, Experiment No.: 870082F1, January 8, 1988.
Other	

Test Substance Test substance: Remarks:	DMCD (<i>trans</i> isomer); CAS No.: 3399-22-2 Purity was unknown, material was stated to have 1.6% of the <i>cis</i> - isomer
Method Method: Test type: GLP: Year: Species/strain: Route of exposure: Duration of test: Exposure levels: Sex: Exposure period: Post-exposure observation period: Remarks:	Other Repeated oral-dose toxicity No 1981 Rat/ Oral 2-Weeks 0, 0.1 and 1.0% in diet Male Continuous in feed for 12 days None Five rats were exposed to trans-DMCD in their diet. Observations were made of body weight, feed consumption, clinical signs, hematology (Hb conc., Hct, RBC count and morphology, WBC count and diff.) and clinical chemistries (AST, ALT, LDH, ALK, Creat., BUN, and gluc.) were conducted. At termination, animals underwent a gross examination with the liver and kidneys weighed and examined histologically.
Results NOAEL (NOEL): Actual doses received: Toxic responses by dose: Statistical methods: Remarks:	1.0%; 1000 mg/kg 0, 97, and 1000 mg/kg There were no mortalities or clinical signs related to exposure. There were no differences in body weights, feed consumption, hematology, clinical chemistries, and organ weights compared to controls. There were no gross or histological changes observed. Not described.
Conclusions	Trans-DMCD induced essentially no toxicity following 2 weeks of exposure at a high exposure rate (1% of diet).
Data Quality Reliability: Remarks:	Reliable with restrictions Only basic data as part of a report summary were available for this study and significant methodological details were not present.
References	Basic Toxicity of <i>trans</i> -Dimethyl-1,4-cyclohexanedicarboxylate. Eastman Kodak Company, Rochester, NY; HS&HFL No.: 80-0296, February 18, 1981.
Other	

C. Genetic Toxicity - Mutation

Test Substance	
Test substance:	1,4-Cyclohexanedicarboxylic acid (CHDA; CAS No.: 1076-97-7)
Remarks:	Purity unknown
Method	
Method:	Other; OECD: TG-471-like
Test type:	<i>In vitro</i> mutagenicity
GLP:	Yes
Year:	1994
Species/strain:	<i>Salmonella typhimurium</i> (strains: TA98, 100, 1535, and 1537) and <i>Escherichia coli</i> (strain: WP2uvrA(pKM101))
Metabolic activation:	Yes; Sprague-Dawley rat liver S9 induced with Aroclor 1254
Concentration tested:	100, 333, 667, 1,000, 3,330, and 5,000 ug/plate
Remarks:	Positive controls: 2-aminoanthracene, 2-nitrofluorene, sodium azide, ICR-191, 4-nitroquinoline-N-oxide. Negative control was the test vehicle dimethylsulfoxide. The study was performed in triplicate at each dose.
Results	
Result:	No positive responses were induced by CHDA in any of the tester strains
Cytotoxic concentration:	No cytotoxicity was observed
Precipitation concentration:	No precipitate was noted.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Specific methods were not noted in the report. However, analyses were not needed due to the absence of an increase in the number of revertants colonies at any dose beyond the positive control.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was well-documented study that followed the basic principles of those outlined in OECD guideline 471 and was conducted under GLP assurances. Data were missing on sample purity.
References	Mutagenicity Test with EC 94-0212, CHDA in the Salmonella – Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay; Hazelton Washington, Vienna, VA; HWA Study No.: 16281-0-409R; September 19, 1994.
Other	

D. Genetic Toxicity – Chromosomal Aberrations

Test Substance Test substance: Remarks:	1,4-Cyclohexanedicarboxylic acid (CHDA; CAS No.: 1076-97-7) Purity unknown
Method Method: Test type: GLP: Year: Species/strain: Concentrations tested: Metabolic Activation: Remarks:	Similar to OECD: TG-473 <i>In vitro</i> mammalian chromosomal aberrations assay Yes 1994 Chinese hamster ovary cells (CHO) 750, 1,000, 1,500, and 2,000 ug/ml Aroclor 1254-induced SD rat liver S9 The positive controls consisted of mitomycin-C and cyclophosphamide. Negative control was the test vehicle dimethylsulfoxide. Assay length was 20.0 hours. Replicate cultures were used at each dose level. Mitotic index was based on metaphase analysis of 1000 cells and aberrations were based on a scoring of 100 cells from each replicate or 200 total.
Results Result: Cytotoxic concentration: Precipitation concentration: Genotoxic effects With activation: Without activation: Statistical methods: Remarks:	No significant increase in cells with aberrations was observed (see remarks) Evidence of cytotoxicity was seen at 2,250 ug/ml A precipitate was observed at the 2,250 ug/ml concentration Negative Negative Statistical analysis employed a test for linear trends and Fisher's Exact Test to compare the percentage of cells with aberrations with an adjustment for multiple comparisons. A confirmatory assay was conducted at dose levels of 500, 1,000, 1,500, 2,000, and 2,250 ug/ml with cells harvested after 20 and 44 hours. Complete toxicity was seen at 2,250 ug/ml without metabolic activation. No increases in aberrations were seen after 20 hours in the non-activation system or at 44 hours with S9 at any dose. However, an increase in aberrations was seen in one of the replicates at the 2,000 ug/ml dose (-S9) at the 44-hour time point and at the 2,250 ug/ml dose with S9 after 20 hours. A significant increase in percent polyploidy was observed at 2,250 ug/ml from the 44-hour assay with activation.
Conclusions	No dose relationship was observed in the assays where a positive response was observed. The positive response for aberrations was observed in only one of the replicate cultures while the Polyploidy response was seen in both. However, severe toxicity was seen at this concentration. Accordingly, the relevance of these effects at a toxic concentration makes its significance questionable.
Data Quality Reliability: Remarks:	Reliable without restrictions This was well-documented study that followed the basic principles of those outlined in OECD guideline 473 and was conducted under GLP assurances. Data were missing on sample purity.
References	Measuring Chromosomal Aberrations in Chinese Hamster Ovary Cells; Hazelton Washington, Vienna, VA; HWA Study No.: 16281-0-437CO; November 1, 1994
Other	

E. Developmental Toxicity

Test Substance Test substance: Remarks:	DMCD (mixed isomers); CAS No.: 94-60-0 Purity was 93.2%
Method Method: GLP: Year: Species/strain: Sex: Route of exposure: Exposure levels: Actual dose levels: Exposure period: Frequency of treatment: Control group and treatment: Duration of test: Remarks:	OECD: TG-421; USEPA: OPPTS 870.3550 Yes 2003 Rats/Sprague-Dawley CRL:CD®(SD)IGS BR Male and Female (12/sex/exposure level) Oral, dietary 0, 1.5, 4.5, and 15.0 mg/g of feed (0.15, 0.45, and 1.5%) Approx. 92, 276, and 888 mg/kg (male), and 111, 351, and 1124 mg/kg (female) 24 hrs/day; Test material in diet was fed <i>ad libitum</i> 7 days/week Controls were exposed to basal diet The study consisted of four phases: pre-mating (14 days); mating (1 to 14 days); pregnancy (21 to 23 days); and early lactation (4 to 6 days). The male rats were treated throughout the study, a period of 50 days. The female rats were treated throughout the study until they were euthanized, a period of approximately 38-57 days. The male rats were euthanized on Day 51. The female rats that delivered a litter, and their offspring, were euthanized on Days 4, 5, or 6 postpartum. Female rats that showed evidence of mating but did not deliver were euthanized on Day 23 of gestation. The study design included the additional endpoints of epididymal spermatozoan numbers and motility, and testicular spermatid head counts.
Results Maternal/Paternal toxicity NOAEL: Repro./Develop. toxicity NOAEL: Parental toxic responses: Postnatal toxic responses:	1.5%; or 888 mg/kg for males and 1124 mg/kg for females 1.5%; or 888 mg/kg for males and 1124 mg/kg for females Male rats that consumed diets containing 15.0 mg/g (1.50%) of the test substance exhibited reduced mean body weights and/or feed consumption values for the duration of the study. However, there were no adverse effects on fertility, histology of the testes and epididymis, or testicular and epididymal sperm counts. No treatment-related effects were seen in male rats from the lower dose groups. There were no treatment-related effects or histopathological alterations seen in female rats from any dose group and there were no biologically significant changes in their offspring. There were no toxicologically significant differences in the reproductive parameters evaluated including reproductive performance, fertility index, fecundity index, precoital interval, gestation duration, numbers of implants, number of corpora lutea, pre- and post-implantation loss, pup survival, live and dead pups, male and female pups, pup body weight and body weight changes. Although the duration of the gestation phase was shorter ($p \leq 0.05$) for female rats from the mid-dose group, there was no apparent effect on pup viability. Mean pup weight change and percent pup weight change from Days 0 to 4 were also significantly ($p \leq 0.05$) higher for pups from the low-dose group when compared with the control group, but these changes were not considered biologically significant.

Statistical Methods:	Homogeneity of data was evaluated using Bartlett's test ($p \leq 0.01$), one-way analysis of variance (ANOVA) ($p \leq 0.05$), and Dunnett's t-test ($p \leq 0.05$) to indicate statistical significance. When the variances of the means were not considered equal by the Bartlett's test ($p \leq 0.01$), the data were evaluated using a Kruskal-Wallis H-test ($p < 0.05$) followed by Mann-Whitney U-test ($p < 0.05$).
Remarks:	The reproductive performance of the dams and the fertility and fecundity indices were evaluated in contingency tables, using a Chi-square test ($p < 0.05$).
Conclusions	DMCD did not affect the reproductive capacity of the adult animals in this study.
Data Quality	
Reliability:	Reliable without restriction
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Reproduction/Developmental Toxicity Screening Test in the Rat. Toxicological Sciences Laboratory; Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; July 2003.
Other	

F. Reproductive Toxicity

Test Substance Test substance: Remarks:	DMCD (mixed isomers); CAS No.: 94-60-0 Purity was 93.2%
Method Method: GLP: Year: Species/strain: Sex: Route of exposure: Exposure levels: Actual dose levels: Exposure period: Frequency of treatment: Control group and treatment: Duration of test: Remarks:	OECD: TG-421; USEPA: OPPTS 870.3550 Yes 2003 Rats/Sprague-Dawley CRL:CD [®] (SD)IGS BR Male and Female (12/sex/exposure level) Oral, dietary 0, 1.5, 4.5, and 15.0 mg/g of feed (0.15, 0.45, and 1.5%) Approx. 92, 276, and 888 mg/kg (male), and 111, 351, and 1124 mg/kg (female) 24 hrs/day; Test material in diet was fed <i>ad libitum</i> 7 days/week Controls were exposed to basal diet The study consisted of four phases: pre-mating (14 days); mating (1 to 14 days); pregnancy (21 to 23 days); and early lactation (4 to 6 days). The male rats were treated throughout the study, a period of 50 days. The female rats were treated throughout the study until they were euthanized, a period of approximately 38-57 days. The male rats were euthanized on Day 51. The female rats that delivered a litter, and their offspring, were euthanized on Days 4, 5, or 6 postpartum. Female rats that showed evidence of mating but did not deliver were euthanized on Day 23 of gestation. The study design included the additional endpoints of epididymal spermatozoan numbers and motility, and testicular spermatid head counts.
Results Maternal/Paternal toxicity NOAEL: Repro./Develop. toxicity NOAEL: Parental toxic responses: Postnatal toxic responses:	1.5%; or 888 mg/kg for males and 1124 mg/kg for females 1.5%; or 888 mg/kg for males and 1124 mg/kg for females Male rats that consumed diets containing 15.0 mg/g (1.50%) of the test substance exhibited reduced mean body weights and/or feed consumption values for the duration of the study. However, there were no adverse effects on fertility, histology of the testes and epididymis, or testicular and epididymal sperm counts. No treatment-related effects were seen in male rats from the lower dose groups. There were no treatment-related effects or histopathological alterations seen in the ovaries of female rats from any dose group and there were no biologically significant changes in their offspring. There were no toxicologically significant differences in the reproductive parameters evaluated including reproductive performance, fertility index, fecundity index, precoital interval, gestation duration, numbers of implants, number of corpora lutea, pre- and post-implantation loss, pup survival, live and dead pups, male and female pups, pup body weight and body weight changes. Although the duration of the gestation phase was shorter ($p \leq 0.05$) for female rats from the mid-dose group, there was no apparent effect on pup viability. Mean pup weight change and percent pup weight change from Days 0 to 4 were also significantly ($p \leq 0.05$) higher for pups from the low-dose group when compared with the control group, but these changes were not considered biologically significant.

Statistical Methods:	Homogeneity of data was evaluated using Bartlett's test ($p \leq 0.01$), one-way analysis of variance (ANOVA) ($p \leq 0.05$), and Dunnett's t-test ($p \leq 0.05$) to indicate statistical significance. When the variances of the means were not considered equal by the Bartlett's test ($p \leq 0.01$), the data were evaluated using a Kruskal-Wallis H-test ($p < 0.05$) followed by Mann-Whitney U-test ($p < 0.05$).
Remarks:	The reproductive performance of the dams and the fertility and fecundity indices were evaluated in contingency tables, using a Chi-square test ($p < 0.05$).
Conclusions	DMCD did not affect the reproductive capacity of the adult animals in this study.
Data Quality Reliability: Remarks:	Reliable without restriction This was a well-documented OECD guideline study conducted under GLP assurances.
References	Reproduction/Developmental Toxicity Screening Test in the Rat. Toxicological Sciences Laboratory; Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; July 2003.
Other	